British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **82** 1509–1516 1509

PHARMACOKINETICS

Pharmacokinetics of oral fludrocortisone in septic shock

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Received 17 January 2016; **Revised** 28 June 2016; **Accepted** 10 July 2016

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Keywords Fludrocortisone, pharmacokinetics, sepsis, shock

AIM

The combination of hydrocortisone and fludrocortisone improved outcomes in septic shock. However, the specific role of fludrocortisone remains controversial and its pharmacokinetics (PK) has never been investigated in septic shock. This study aimed at characterizing the PK of fludrocortisone in septic shock.

METHODS

This was a single-centre ancillary PK study of a large multinational trial of crystalloids versus colloids for acute hypovolemia in intensive care unit (ICU) patients. In 21 adults with septic shock, fludrocortisone plasma concentrations were measured by liquid chromatography–mass spectrometry tandem analysis, before and repeatedly until 18 h after an oral dose of 50 μg. PK parameters were estimated using a nonlinear mixed-effects modelling.

RESULTS

Undetectable plasma concentrations were observed in 7 out of 21 patients. In the remaining 14 patients, plasma fludrocortisone concentrations were best described by a one-compartmental model with first-order absorption, a lag time (T_{lag}) before the absorption phase, and first-order elimination. Severity of illness, as quantified by Simplified Acute Physiology Score II, significantly increased T_{lag} and apparent clearance. There was a large inter-individual variability in PK parameters. The population estimates of PK parameters (inter-individual variability) were: T_{lag} 0.65 h (98%), apparent clearance 40 l h^{-1} (49%) and apparent volume of distribution 78 l (75%). Plasma half-life was estimated at 1.35 h (95% CI, 0.84–2.03) and area under the curve of plasma concentrations was estimated at 1.25 μg h l^{-1} (95% CI, 1.09–1.46).

CONCLUSIONS

A single oral dose of fludrocortisone yielded undetectable plasma concentrations in one-third of adults with septic shock. Fludrocortisone PK showed a short plasma elimination half-life and a large inter-individual variability.

DOI:10.1111/bcp.13065

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Low doses of corticosteroids improves outcomes in septic shock but the effectiveness of fludrocortisone is debated.
- The pharmacokinetics of fludrocortisone in septic shock patients has never been studied.

WHAT THIS STUDY ADDS

- This study shows that one third of our septic patients had undetectable fludrocortisone plasma concentrations after oral administration.
- The pharmacokinetics of oral fludrocortisone shows a large inter-individual variability and a short plasma elimination half-life.

Table of Links

LIGANDS
fludrocortisone
hydrocortisone / cortisol
sufentanil

This Table lists key ligands in this article, which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1].

Introduction

Septic shock is the most severe complication of infection. Its incidence is about 300 per 100 000 inhabitants worldwide [2, 3]. Its mortality rate ranges from 20 to 40% in the short term, and rises up to 60% in the long term [2, 3]. About half of survivors may develop long-term sequelae [2]. Corticosteroids may improve patient morbidity and mortality [4]. Current Surviving Sepsis Campaign guidelines suggest giving moderate doses of corticosteroids in catecholamine-dependent septic shock [5].

Though one large randomized controlled trial showed the benefit of a combination of hydrocortisone and fludrocortisone [4], the role of fludrocortisone remains controversial [5]. In particular, the pharmacokinetics of fludrocortisone given orally in septic shock has not been investigated so far.

Fludrocortisone is usually given in its acetate form as an inactive pro-drug that requires hydrolization. Hydrolysis by esterases or pseudoesterases may occur in body fluids and mainly in the liver but may be only partial.

Our group has recently developed a robust and sensitive assay for measuring plasma levels of active fludrocortisone concentrations [6]. In the current study, we investigated in adults with septic shock the absorption of fludrocortisone given orally and its pharmacokinetics.

Materials and methods

Patients and settings

This study was ancillary to the CRISTAL study [7]. This trial was a multinational randomized controlled trial of crystalloids versus colloids resuscitation for acute hypovolemia in intensive care unit (ICU) patients. In this trial, randomization was stratified according to patient's case mix (sepsis, trauma or hypovolemic shock without sepsis or trauma). This trial was registered in clinicaltrial.gov (NCT00318942) and was approved by ethics committee and regulatory agencies according to national legislation. For France, the study protocol was approved by the Committee for the Protection of People of Saint-Germain-en-Laye with waiver of consent. The CRISTAL trial recruited patients from February 2003 to August 2012. CRISTAL study patients with evidence of septic shock [8] were recruited for this ancillary study at Raymond Poincaré Hospital (Garches, France) from December 2010 to May 2012 (corresponding with the completion of the CRISTAL study). Thus, there was no planned sample size for this ancillary study. Criteria for septic shock included: (i) clinically or microbiologically documented source of infection; (ii) at least two of the following signs of tissue hypoperfusion/organ dysfunction: urinary output < 20 ml h^{-1}, Glasgow coma score < 10, need for mechanical ventilation, arterial lactate levels > 2 mmol l^{-1}; (iii), need for vasopressor therapy to maintain a systolic blood pressure > 90 mmHg or a mean blood pressure > 65 mmHg. Patients with known endocrine disorders or any condition or treatment that may have affected cortisol synthesis or metabolism [9] were excluded.

Patients were managed according to the 2008 edition of the Surviving Sepsis Campaign guidelines [10]. They received both hydrocortisone 50 mg four times per day and fludrocortisone 50 μg daily for seven days. Within the first three hours of septic shock onset and prior to any corticotherapy, 50 μg of fludrocortisone were given via a naso-gastric tube as previously reported [4]. Whole blood was sampled (7 ml) from an arterial access before fludrocortisone administration and every 30 min for 6 h, then hourly for 18 h. Plasma was separated by centrifugation at 5000 tr min^{-1} for 10 min and kept frozen at −80°C until analysis.

Blood sample analysis

Sensitive quantification of fludrocortisone in plasma was obtained by a solid-phase extraction using Oasis®-HLB

cartridge, followed by liquid chromatography–mass spectrometry tandem (LC–MS/MS) analysis as described elsewhere [6]. This LC–MS/MS method allows very low fludrocortisone plasma concentrations with a lower limit of quantification of 0.10 $\mu g\,l^{-1}$ to be analysed.

Data analysis

Patient characteristics. To investigate reasons for a possible non-absorption of fludrocortisone, we compared patients with detectable ($\geq 0.10\,\mu g\,l^{-1}$) and undetectable ($< 0.10\,\mu g\,l^{-1}$) fludrocortisone plasma levels on demographic data, severity of illness, concomitant therapies, and hemodynamic and biological status. Wilcoxon test for quantitative variables and Fisher exact test for categorical variables were used to compare the two groups. The statistical analysis was performed using R statistical software [11].

Population pharmacokinetic analysis. Nonlinear mixed effects modelling was used to analyse the pharmacokinetic data, using the Stochastic Approximation Expectation Maximization (SAEM) algorithm implemented in MONOLIX 4.3.0 software (LIXOFT, France) as previously described [12]. The algorithm takes into account censored data (below the quantification limit) for the estimation of maximum likelihood and structural parameters [13]. The inter-individual variability was described by an exponential variance model as follows:

$$\theta_i = \theta_{pop} \cdot \exp(\eta_i)$$

where θ_i and θ_{pop} are individual and population parameters, respectively; η describes the inter-individual variability, which was assumed to be normally distributed around zero with a standard deviation ω_θ, by which the ith individual's parameter differed from the average population value (θ_{pop}). A diagonal variance–covariance matrix of parameters (Ω) was used.

A basic population pharmacokinetic model without covariates was first developed. For the structural pharmacokinetic model, one- and two-compartment models with zero- or first-order absorption and first-order elimination were compared. A model with lag time in the absorption phase was also tested. The likelihood ratio test (assessing the likelihood ratio against a χ^2 distribution, LL = $-2 \times$ log-likelihood) was used to compare nested structural models and to select the best one. The model with the significantly smallest LL (a difference $\Delta LL > 3.84$ between the nested models was considered statistically significant) was selected [14].

From the basic model, nine covariates were studied and chosen for their impact on pharmacokinetic parameters. These covariates were: age, gender, total body weight, Simplified Acute Physiology Score II (SAPSII) [15], serum levels of total protein, albumin, creatinine, diuresis and proton pump inhibitors. A reduction of LL by 3.84 ($P < 0.05$) for forward inclusion and an increase of LL by 6.64 ($P < 0.01$) for backward elimination were the criteria for retaining a covariate in the model. The parameter–covariate relationships were modelled multiplicatively by the following equations (the first equation for continuous and the second one for binary covariates):

$$\theta_i = \theta_{pop} \cdot \exp(\eta_i) \cdot (Cov_i / \text{median}\,(Cov_i))^{\wedge \beta}$$

$$\theta_i = \theta_{pop} \cdot \exp(\eta_i) \cdot (\beta'^{\wedge\, Cov_i'})$$

where Cov_i and Cov_i' are the values of the continuous and binary (= 0 or 1) covariates in patient i, respectively; β and β' are the respective estimated parameters describing the magnitude of the covariate–parameter relationships.

Several residual error models (additive, proportional and combined) were investigated to describe residual variability. The residual model with the significantly smallest Bayesian Information Criterion was chosen.

The elimination half-life time ($t_{1/2}$) and the area under the curve extrapolated from zero to infinity ($AUC_{0-\infty}$) of plasma concentrations of fludrocortisone were calculated from the following equations:

$$t_{1/2} = \ln(2) \cdot (V/F)/(CL/F)$$

$$AUC_{0-\infty} = \text{Dose}/(CL/F)$$

where $V\,F^{-1}$ is the apparent volume of distribution and $CL\,F^{-1}$ is the apparent plasma clearance, both issued from the population pharmacokinetic parameters of the final model.

Goodness-of-fit of the final model was evaluated using a graphic approach by visual examination of a plot of observed concentrations *vs*. predicted ones and a plot of normalized prediction distribution error (NPDE) *vs*. time [16]. Model validation was performed by visual predictive check (VPC) using simulations. Predicted plasma concentrations of fludrocortisone were calculated based on the randomly sampled pharmacokinetic parameter values and residual variability. Several simulations were performed and 80% confidence intervals (i.e., 10th and 90th percentiles) were computed from simulated pharmacokinetic profiles and compared with the median and the 10th and 90th percentiles of observed pharmacokinetic profiles. The predictive performance of the final model was considered acceptable if the majority of original data points were contained inside predicted confidence intervals, with no major systematic deviation between simulated and observed data.

Complementary analysis. In a further exploratory analysis, correlations between fludrocortisone plasma levels and mean blood pressure, heart rate, urinary and plasma sodium and potassium levels at different time-points were tested by means of Pearson or Spearman correlation coefficients as appropriate. STATA software, Version 11.1 data analysis and statistical software (StataCorp LP, College Station, TX, USA) was used for statistical analysis.

Results

Patient characteristics

Twenty-one patients were included in this ancillary study. One-third (7 out of 21 patients) had undetectable fludrocortisone plasma concentrations. Table 1 displays the

Table 1

Characteristics of patients with detectable (≥0.10 μg l^{-1}) and undetectable (< 0.10 μg l^{-1}) fludrocortisone plasma concentrations before administration

Variables	Patients with detectable fludrocortisone plasma concentrations		
	Yes (*n* = 14)	No (*n* = 7)	*P*
Age (years)	65 (57–75)	55 (54–65)	>0.10
Male sex	8 (57)	2 (29)	>0.10
Weight (kg)	71 (60–84)	64 (62–69)	>0.10
Severity			
Severity Acute Physiologic Score II	53 (35–68)	42 (37–50)	>0.10
Sequential organ failure assessment	11.5 (9.3–14.0)	11.0 (10.0–12.5)	>0.10
Septicemia	0 (0)	3 (43)	0.02
Disseminated intravascular coagulation	5 (36)	2 (29)	>0.10
Diuresis (ml 24 h^{-1})	1205 (124–1470)	800 (490–1807)	>0.10
Heart rate (beats min^{-1})	102 (87–125)	91 (78–101)	>0.10
Mean arterial pressure (mmHg)	76.5 (70.3–89.7)	89.0 (74.0–94.5)	>0.10
Concomitant treatments			
Sedation	11 (79)	3 (43)	>0.10
Sufentanyl (μg hr^{-1})	10.0 (1.8–18.7)	10.0 (0.0–12.5)	>0.10
Catecholamine dose (μg kg^{-1} min^{-1})	0.10 (0.06–0.50)	0.29 (0.08–0.29)	>0.10
Proton pump inhibitor	9 (64)	7 (100)	0.06
Blood biological markers			
Alanine aminotransferase (IU l^{-1})	69 (44–370)	34 (30–55)	>0.10
Aspartate aminotransferase (IU l^{-1})	97 (50–192)	39 (27–162)	>0.10
Lactate (mmol l^{-1})	2.05 (1.52–3.57)	2.20 (1.45–3.15)	>0.10
Protein (g l^{-1})	52.5 (38.5–60.0)	47.0 (41.5–52.0)	>0.10
Albumin (g l^{-1})	18.0 (16.0–21.5)	16.5 (12.7–18.0)	>0.10
Haemoglobin (g/dl)	8.75 (7.47–9.92)	7.20 (6.65–7.95)	0.06
Cortisol (μg l^{-1})	605 (235–1161)	337 (82–339)	>0.10
Creatinine (μmol l^{-1})	114 (77–242)	114 (57–124)	>0.10
Urea (mmol l^{-1})	7.7 (5.0–16.4)	7.8 (3.3–11.6)	>0.10
Death in ICU	7 (50)	4 (57)	>0.10

Continuous variables are expressed as medians (25th percentile–75th percentile); qualitative variables are expressed as number (%)
Data were available for 21 patients except for albumin (*n* = 10 + 6) and cortisol (*n* = 12 + 5)
IU, international unit

main baseline characteristics of patients with detectable (≥ 0.10 μg l^{-1}) and undetectable (< 0.10 μg l^{-1}) fludrocortisone plasma levels. There was no major difference between the two groups of patients except a higher rate of septicemia, i.e. patients with positive blood cultures ($P = 0.02$), and a trend towards a higher rate of patients receiving proton pump inhibitors and lower haemoglobin blood level ($P = 0.06$ for both) in the group with undetectable fludrocortisone plasma concentrations.

Population pharmacokinetic analysis

A comparison of fits of each of tested structural mathematical models indicated that fludrocortisone plasma concentrations were best described by a one-compartmental model. This model was parameterized in terms of apparent clearance (CL F^{-1}; l h^{-1}), apparent volume of distribution (V F^{-1}; L), and first-order absorption rate constant (k_a; h^{-1}) with a lag time before the absorption phase (T_{lag}; h). A proportional model was selected to describe residual variability. Among tested covariates, inclusion of SAPSII was found to significantly increase T_{lag} ($\Delta LL = -4.35$, $P = 0.037$) and CL F^{-1} ($\Delta LL = -8.22$, $P = 0.004$). Thus the effect of SAPSII on the two parameters was retained in the final model.

Final pharmacokinetic parameter estimates, inter-individual variability, residual variability and covariate effects are presented in Table 2. All parameters were reliably

Table 2

Parameter estimates from the final pharmacokinetic model of oral fludrocortisone

Parameter	Description	Estimate	R.S.E (%)	P[a]
Population parameter				
k_a (h^{-1})	Oral absorption rate constant	0.67	23	
V F^{-1} (l)	Apparent volume of distribution	78	28	
CL F^{-1} (l h^{-1})	Apparent clearance	40	15	
T_{lag} (h)	Lag time in the absorption phase	0.65	34	
Inter-individual variability[b]				
ω_k_a (%)		42	36	
ω_V F^{-1} (%)		75	23	
ω_CL F^{-1} (%)		49	23	
ω_T_{lag} (%)		98	24	
Covariate effect[b]				
$\beta\_(T_{lag} \sim SAPSII)$		0.036	39	0.037
$\beta\_(CL\ F^{-1} \sim SAPSII)$		0.019	35	0.004
Residual variability				
σ_{prop}		0.20	25	
Secondary parameters				
$t_{1/2}$ (h)	Time to plasma half-life	1.35 $CI_{95\%}$ (0.84–2.03)		
$AUC_{0-\infty}$ (μg h L^{-1})	Area under curve from t_0 to t_∞	1.25 $CI_{95\%}$ (1.09–1.46)		
C_{max} (μg l^{-1}) (Mean ± SD)	Maximum observed concentration	0.19 ± 0.11		
T_{max} (h) (Mean ± SD)	Time to C_{max}	2.92 ± 0.74		

$CI_{95\%}$, confidence interval of 95%; RSE, relative standard error; SAPSII, Simplified Acute Physiology Score II (covariate); SD, standard deviation; σ_{prop}, variance parameter of proportional residual model as follows: $C_{observerd,ij} = C_{predicted,ij} + C_{predicted,ij} * \varepsilon_{prop,ij}$ with $\varepsilon_{prop} \sim N(0, \sigma_{prop})$.
[a]*P* values from the likelihood ratio test (comparison between model without *vs.* model with the covariate)
[b]$\theta_i = \theta_{population} * \exp(\eta_i) * (SAPSII_i/\text{median}(SAPSII))\ \hat{}\ \beta\_(\theta \sim SAPSII)$, where θ is the parameter CL F^{-1} or T_{lag}, *i* indicates the *i*th individual and $\eta \sim N(0, \omega\_\theta)$

estimated as reflected by the small relative standard errors (RSEs < 40%). Mean population pharmacokinetic parameter estimations were: CL F^{-1} = 40 l h^{-1}, V F^{-1} = 78 l, k_a = 0.67 h^{-1} and T_{lag} = 0.65 h. A large inter-individual variability in pharmacokinetic parameters was observed particularly on V F^{-1} and T_{lag} (75% and 98%, respectively). Mean ± standard deviation peak plasma concentration was 0.19 ± 0.11 μg l^{-1} and was achieved 2.92 ± 0.74 h after administration. Plasma half-life was estimated at 1.35 h (95% CI, 0.84–2.03) and $AUC_{0-\infty}$ at 1.25 μg h l^{-1} (95% CI, 1.09–1.46).

Goodness-of-fit plots of the final pharmacokinetic model including SAPSII as covariate are shown in Figure 1. The model adequately described the observations as shown by the plots of observations *vs.* population predictions and *vs.* individual predictions. Moreover, the VPC (Figure 2) and NPDE *vs.* time plots (Figure 1, C) indicate a good predictive performance of the model.

Fludrocortisone effects

Fludrocortisone plasma levels did not correlate with mean blood pressure, heart rate and urinary sodium and potassium levels. Significant associations were found between plasma levels of fludrocortisone and sodium 2.50 h after administration (r = 0.74, P = 0.03) and between plasma levels of fludrocortisone and potassium 4.50 h after administration (r = −0.58, P = 0.02) of fludrocortisone.

Discussion

The current study showed that a single oral administration of 50 μg of fludrocortisone resulted in detectable plasma concentrations in two-thirds of adults with catecholamine-dependent sepsis. In these patients, we found that fludrocortisone concentrations were best described by a one-compartmental model with first-order absorption, lag time, and first-order elimination. The peak plasma concentration was obtained almost 3 h after administration. Plasma half-life was short (around 1 h). Severity of illness, as quantified by SAPSII score, delayed the time of absorption and increased the apparent clearance.

No data has previously been published on the pharmacokinetics of fludrocortisone in septic shock patients. The only

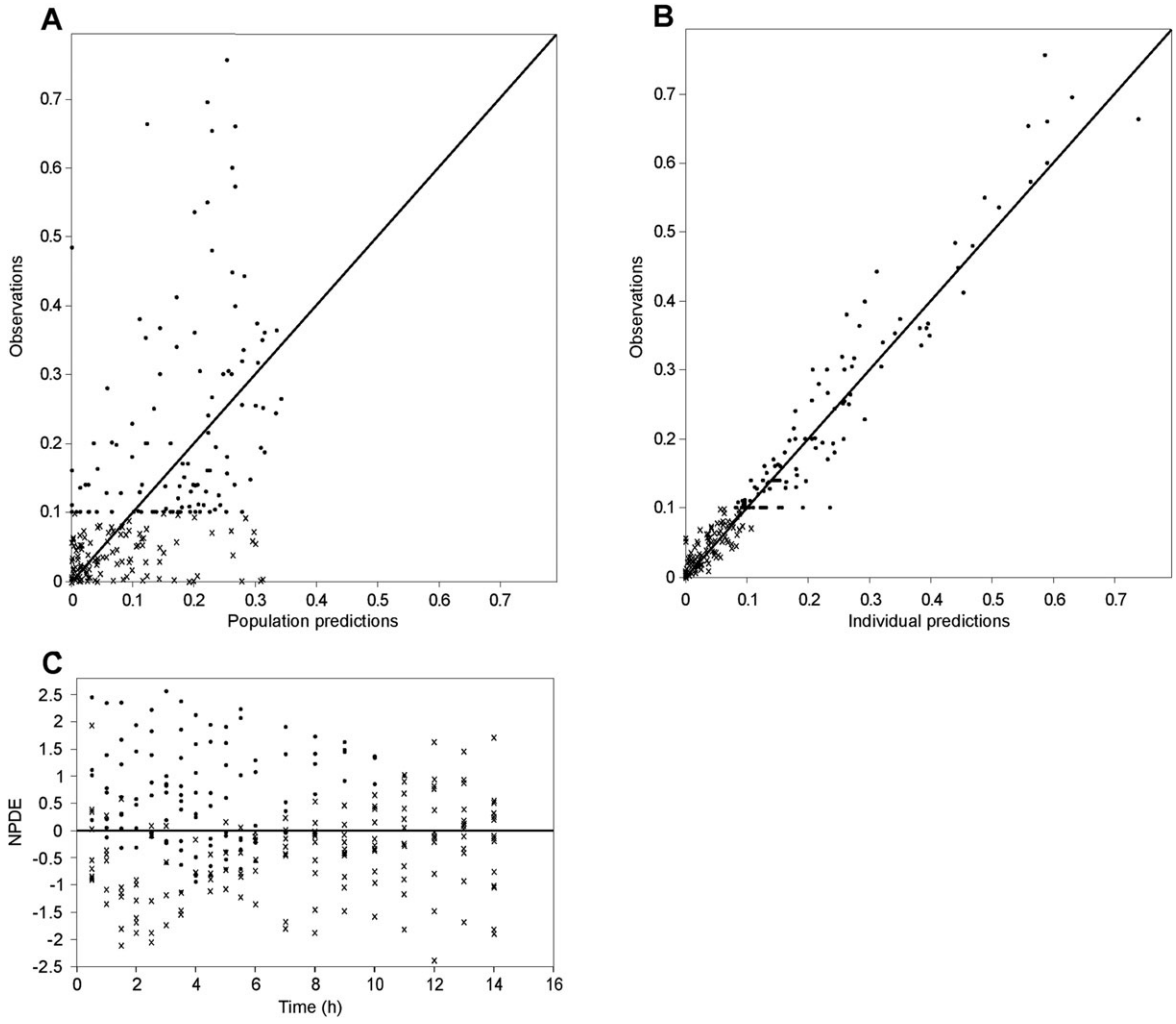

Figure 1

Goodness-of-fit plots for the final pharmacokinetic model with Simplified Acute Physiology Score II (SAPSII) covariate. (A) Observations *vs.* population predicted values. (B) Observations *vs.* individual predicted values. (C) Normalized Prediction Distribution Error (NPDE) *vs.* time. Observations are plotted as closed circles and censored data (below the quantification limit) as crosses

available data were assessed in healthy volunteers but using higher single doses (between 100 μg and 2 mg) and found a wide range of plasma half-lives between 0.5 h and 3.6 h [17–19]. Our results are in this range of values (1.35 h), suggesting that fludrocortisone elimination is similar in septic shock patients and in healthy volunteers. However, contrary to previous studies, a population approach (non-linear mixed effects models) was used in the current study allowing the quantification of the inter-individual variability and the influence of covariates on pharmacokinetic parameters. Similar pharmacokinetic modelling in healthy volunteers using the same approach is therefore needed to properly assess whether septic shock affects fludrocortisone pharmacokinetics. Fludrocortisone concentrations were associated with biological mineralocorticoid activity as shown by a significant positive correlation with plasma sodium levels and a significant negative correlation with plasma potassium levels. These results are consistent with the findings of Laviolle *et al.*, who showed sodium and potassium modification between 6 and 12 h after fludrocortisone administration [20]. These results are also in keeping with the observed higher increase (>5 mmol l^{-1} from baseline) of plasma sodium concentrations in the Ger-Inf trial that investigated 200 mg of hydrocortisone combined with 50 μg of fludrocortisone [4] than in the CORTICUS trial (2 mmol l^{-1} from baseline) that investigated 200 mg of hydrocortisone alone [21].

One-third of our patients had undetectable fludrocortisone plasma levels that could reflect a lack of absorption in these patients, and which was not explained by the severity of illness. Indeed, fludrocortisone plasma levels were independent of the severity of shock as assessed by lactate levels, mean blood pressure or the amount of vasopressor therapy to maintain mean blood pressure. Likewise, fludrocortisone plasma levels were not dependent on hepato-splanchnic function as assessed by hepatic enzymes and proteins. The current study also suggests that proton pump inhibitors may alter fludrocortisone absorption. Detection of fludrocortisone 40 minutes after enteral administration suggests that the

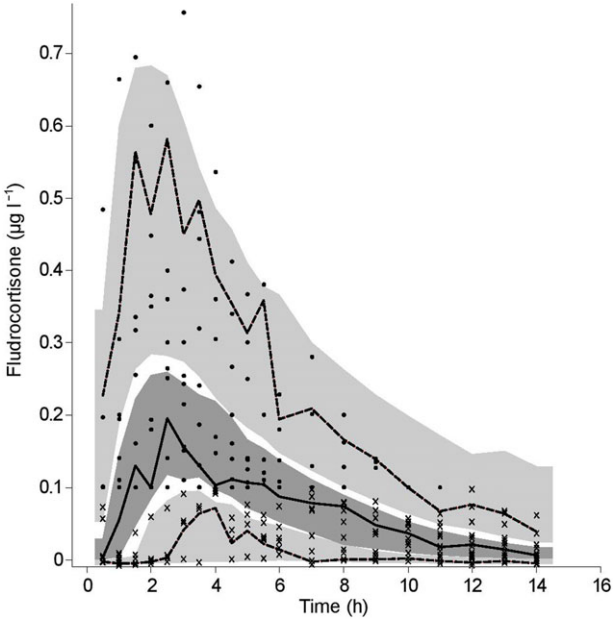

Figure 2

Visual predictive check for the final pharmacokinetic model with Simplified Acute Physiology Score II (SAPSII) covariate. Continuous line represents median observed values and dashed lines represent 10th and 90th observed percentiles. Shaded areas show corresponding prediction intervals calculated from simulated data. Observations are plotted as closed circles and censored data (below the quantification limit) as crosses

absorption occurs mainly in the stomach. We administered fludrocortisone acetate. It is known that acetate crosses the gastric barrier in its non-ionized form [22]. Because the ionization of acetate is dependent on gastric pH and that its uptake is stimulated by low mucosal pH [23], concomitant therapy with proton pump inhibitors may accelerate acetate ionization [24] and therefore reduce fludrocortisone bioavailability.

This work has some limitations. We investigated the pharmacokinetics of fludrocortisone after a single administration of 50 µg. Thus the pharmacokinetics of fludrocortisone given daily for 7 days as suggested in septic shock [5] remains to be investigated. In addition, as one-third of the patients had undetectable plasma fludrocortisone concentration, the pharmacokinetic parameters were estimated in only two-thirds of the patients. However, the population approach allowed us to build a model with good predictive performance as assessed by goodness-of-fit plots.

Conclusion

This work demonstrated that a single 50 µg oral dose of fludrocortisone yielded detectable plasma drug concentrations in two-thirds of adults with septic shock. The main factors preventing fludrocortisone absorption may be the use of pump proton inhibitors and anaemia. Fludrocortisone pharmacokinetics showed a short plasma elimination half-life and a large inter-individual variability.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors

Andrea P. designed and performed the research, interpreted the data and drafted the manuscript. N.H. analyzed and interpreted the pharmacokinetic data and drafted the manuscript. M.R. designed and performed the research and interpreted the data. Angelo P. analysed and interpreted the data. B.L. and E.B. interpreted the data and revised the manuscript. DA designed the research, took responsibility for the study, interpreted the data and drafted the manuscript. J.C.A. designed the research, interpreted the data and revised the manuscript. The first three authors contributed equally to this work.

References

1 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44: D1054–68.

2 Annane D, Sharshar T. Cognitive decline after sepsis. Lancet Respir Med 2015; 3: 61–9.

3 Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013; 369: 840–51.

4 Annane D, Sébille V, Charpentier C, Bollaert P-E, François B, Korach J-M, *et al*. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002; 288: 862–71.

5 Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al*. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013; 39: 165–228.

6 Ribot M, Polito A, Grassin-Delyle S, Annane D, Alvarez J-C. Human plasma quantification of fludrocortisone using liquid chromatography coupled with atmospheric pressure chemical ionization mass spectrometry after low-dosage administration. Clin Chim Acta 2013; 420: 109–13.

7 Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declère AD, *et al*. Effects of fluid resuscitation with colloids *vs*. crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA 2013; 310: 1809–17.

8 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20: 864–74.

9 Oelkers W. Adrenal insufficiency. N Engl J Med 1996; 335: 1206–12.

10 Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, *et al*. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008; 34: 17–60.

11 Team RC. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2012.

12 Chan PLS, Jacqmin P, Lavielle M, McFadyen L, Weatherley B. The use of the SAEM algorithm in MONOLIX software for estimation of population pharmacokinetic-pharmacodynamic-viral dynamics parameters of maraviroc in asymptomatic HIV subjects. J Pharmacokinet Pharmacodyn 2011; 38: 41–61.

13 Beal SL. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn 2001; 28: 481–504.

14 Bertrand J, Comets E, Mentre F. Comparison of model-based tests and selection strategies to detect genetic polymorphisms influencing pharmacokinetic parameters. J Biopharm Stat 2008; 18: 1084–102.

15 Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270: 2957–63.

16 Comets E, Brendel K, Mentré F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. Comput Methods Programs Biomed 2008; 90: 154–66.

17 Banda J, Lakshmanan R, Prasad S, Gudla SP, Prudhivi R. A highly sensitive method for the quantification of fludrocortisone in human plasma using ultra-high-performance liquid chromatography tandem mass spectrometry and its pharmacokinetic application. Biomed Chromatogr BMC 2015; 29: 1213–9.

18 Mitsky VP, Workman RJ, Nicholson WE, Vernikos J, Robertson RM, Robertson D. A sensitive radioimmunoassay for fludrocortisone in human plasma. Steroids 1994; 59: 555–8.

19 Vogt W, Fischer I, Ebenroth S, Appel S, Knedel M, Lücker PW, *et al*. [Pharmacokinetics of 9-fluorhydrocortisone]. Arzneimittelforschung 1971; 21 (Suppl): 1133–43.

20 Laviolle B, Le Maguet P, Verdier M-C, Massart C, Donal E, Lainé F, *et al*. Biological and hemodynamic effects of low doses of fludrocortisone and hydrocortisone, alone or in combination, in healthy volunteers with hypoaldosteronism. Clin Pharmacol Ther 2010; 88: 183–90.

21 Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, *et al*. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008; 358: 111–24.

22 Bugaut M. Occurrence, absorption and metabolism of short chain fatty acids in the digestive tract of mammals. Comp Biochem Physiol B 1987; 86: 439–72.

23 Aschenbach JR, Bilk S, Tadesse G, Stumpff F, Gäbel G. Bicarbonate-dependent and bicarbonate-independent mechanisms contribute to nondiffusive uptake of acetate in the ruminal epithelium of sheep. Am J Physiol Gastrointest Liver Physiol 2009; 296: G1098–G1107.

24 Pohl O, Osterloh I, Lecomte V, Gotteland J-P. Changes in gastric pH and in pharmacokinetics of ulipristal acetate – a drug–drug interaction study using the proton pump inhibitor esomeprazole. Int J Clin Pharmacol Ther 2013; 51: 26–33.